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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,666	09/29/2003	Mike Clark	PHOE0001-100	5283

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,666	CLARK, MIKE	
	Examin r	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *23-24, 26-29, 32-40, and 44-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25,30,31 and 41-43* is/are rejected.

7)☒ Claim(s) *3-4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/15/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on 10/22/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Additionally, Applicant's request to rejoin Group II with Group I is not granted. In the instant, both inventions are patentably distinct from one another. As set forth in the previous office action, a search for the treating population encompassed by the invention of Group I would not overlap with the treating population of Group II, hence, yielding a different field of search. It is recognized that the treating population of Group I and Group II may overlap, however, the level of coextensiveness is not known at the instant; Thus, at the instant, are considered as patentably distinct. Should during examination the Examiner finds that a search for the treating populations of Group I and II overlaps extensively, wherein a serious burden would not be imposed on the Examiner, the Examiner will merge the two Groups into one invention. However, from the search that can be envisioned by the Examiner, a search for one population would not overlap with another population; thereby, requiring a different field of search.

Claims Status

2. Claims 1-51 are pending. Claims 23-24, 26-29, 32-40 and 44-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/22/2004. Claims 1-22, 25, 30-31 and 41-43 are currently under examination.

Claim obj ction

3. Claim 3 recites the limitation "other antiviral compounds" in line 2. There is insufficient antecedent basis for this limitation in the claim. Currently, claim 3 depends on claim 1, however, claim 1 does not specifically recite of an antiviral compound. Because claim 1 does not recite of an antiviral compound, it is determine that the limitation "other antiviral compounds" lacks proper antecedent basis.

4. Claim 4 is objected to because of the following informalities: the claim lacks a "." at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite for the following recitations: "less than about" and "at least 50% in greater than 50% of cells". It is unclear what the metes and bounds are of less than about. The use of "less than" and "about" is not indefinite, however, the combined use of the terms is indefinite because it is unclear what the lower and upper values of a "less than about" range. Additionally, it is unclear what is intended by the recitation and "at least 50% in greater than 50% of cells". No meaningful derivation can be derived from the recitation.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-22, 25, 30-31 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **use** the invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims recite a method of inhibiting replication of one or more viruses in an individual comprising administering to said individual a composition comprising an arginine

deiminase (ADI) bonded to polyethylene glycol (PEG) in an amount effective to inhibit viral replication in said individual.

The nature of the invention is directed at the administration of arginine deiminase bonded to polyethylene glycol as an antiviral agent to inhibit viral replication.

The claims are directed toward a large genus of genotypically and phenotypically disparate viruses, such as viruses from the following viral family: picornaviridae, caliciviridae, astroviridae, togaviridae, flaviviridae, coronaviridae, arteriviridae, rhabdoviridae, filoviridae, paramyxoviridae, orthomyxoviridae, bunyaviridae, arenaviridae, bornaviridae, reoviridae, retroviridae, polyomaviridae, papillomaviridae, adenoviridae, parvoviridae, herpesviridae, poxiviridae, and hepadnaviridae.

Thus, the claimed invention is directed at the inhibition of viral replication via the administration of a universal antiviral agent, ADI-PEG.

The specification speculates on a mechanism of action for ADI-PEG to inhibit viral replication-- by lowering extracellular arginine, which inhibits nitric oxide synthesis; however, such disclosure is not sufficient to enable the skilled artisan to practice the claimed invention without an undue burden of experimentation. This is so because the role of nitric oxide in viral replication is not definitive as Applicant alleged. The art recognized nitric oxide (NO) as an important biologically active molecule that plays a key part in host defense against bacteria, protozoa, and tumour cells. Torre et al., in a review article, discusses the role of NO in the pathogenesis of HIV-1 infection, inasmuch as its role against HIV-1 is unequivocal in inhibiting or increasing viral replication. Torre et al. summarizes that although NO surely plays

an important part in HIV-1 infection, that role is sometimes helpful and other times damaging to the host.[1]

The working examples teach how to make ADI-PEG. The working examples do not provide any evidence that ADI-PEG is effective as an antiviral agent. Working examples number 7 and 8 are directed at an antiviral activity study of ADI-PEG against HCV. However, the examples failed to demonstrate that ADI-PEG is effective against HCV replication. This is due to the cell line that is employed in the working examples, hepatoblastome cell line. It is well known in the art that ADI kills hepatoblastome cells in vitro and in vivo.[2] Thus, in the working examples, the cells are killed by ADI-PEG, and in the absence of viable cells, viral replication is limited. The working examples only reaffirms the knowledge that is well known and accepted in the art, ADI kills hepatoblastome cells. The working examples fail to demonstrate that ADI-PEG inhibits viral replication.

It is well known in the art that antiviral development is not a trivial undertaking. Antiviral development frequently requires in vitro, in vivo, and preliminary clinical studies to truly ascertain the efficacy of any given antiviral compound, as evidenced by Oberg et al.[3] Oberg et al. teaches several antiviral drug screening processes, wherein each process is directed at a specific category of viruses. The general outline of each process includes in vitro studies, in vivo animal studies, safety evaluations and clinical trials. Oberg et al. also notes that the validity of different animal models can only be determined by evaluation of antiviral activity in patients. The teaching of Oberg et al. is also exemplified by Saunders[4]

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[1] Torre et al. Role of nitric oxide in HIV-1 infection: friend or foe? Lancet Infect Dis. 2002 May; 2(5): 273-80.
[2] Izzo et al. Pegylated arginine deiminase treatment of patients with unresectable hepatocellular carcinoma: results from Phase I/II studies. Journal of Clinical Oncology. 05/2004, Vol. 22, No. 10, pp. 1815-1822.
[3] Oberg et al. Screening for new agents. Eur. J. Clin. Microbiol. Infect Dis., July 1990, Vol. 9, No. 7, p. 466-471.
[4] Saunders. Non-nucleoside inhibitors of HIV reverse transcriptase: screening successes-clinical failures. Drug Design and Discovery. 1992, Vol. 8, pp. 255-263.

and Yarchoan et al.[5] Saunders teaches of antiviral that has demonstrated to be successful against viral replication in the screening process has proven to be failures in clinical trials. Yarchoan et al. teaches that in vitro antiviral activity does not correlate with in vivo antiviral activity. Ergo, in the instant art, it is clear that in vitro data does not necessarily correlate with in vivo data and/or clinical observation. Furthermore, it is also well known in the art that the inhibitory activity of an antiviral agent against a particular virus cannot be equated with its inhibitory effect against another virus.[6]

Thus, in view of the analysis above, the skilled artisan in the art would not be able to practice the claimed invention without an undue burden of experimentation. The claimed invention is found not enabling.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

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[5] Yarchoan et al. Correlations between the in vitro and in vivo activity of anti-HIV agents: implications for future drug development. J. Enzyme Inhibition. 1992, Vol. 6, pp. 99-111.
[6] Wiltink et al. Antiviral drugs. Pharmaceutisch Weekblad Scientific edition. 1991, Vol. 13, No. 2, pp. 58-69.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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